

Un-Sustained Response to Benralizumab in Eosinophilic Asthma with Previous 3-Year Mepolizumab Administration

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Eosinophils play pivotal roles in the inflammatory processes of asthma, and have been the target of new biologic treatments for eosinophilic asthma. Benralizumab is the monoclonal antibody (mAb) that targets α chain of the interleukin 5 (IL-5) receptor, and mepolizumab is the anti-IL-5 mAb. We herein present a patient with eosinophilic asthma who showed un-sustained response to benralizumab after 3-year mepolizumab administration.

A 42-year-old woman, never smoker, visited the clinic because of increasing dyspnea on January 22, 2016. She was treated with pranlukast 450mg/day and fluticasone/formoterol 125 μ g/5 μ g inhaler 2 puffs/day. Because of unstable respiratory symptoms, she was given systemic steroids occasionally. On February 27, 2016, the patient was introduced to the hospital by the experienced pulmonologist.

We confirmed the diagnosis of asthma using the Global Initiative for Asthma guidelines [1]. Forced expiratory volume in 1 second (FEV₁) was 74.1 % of the predicted value with an increase of 14.1 % in FEV₁ after 180 μ g salbutamol inhaler. She was a non-allergic asthma patient, diagnosed with serum total IgE level 94 IU/mL and negative results of specific IgE for common inhaled allergens including *Dermatophagoides farinae* and *pteronyssinus*. Her regimen was changed to budesonide/formoterol 160 μ g/4.5 μ g inhaler 8 puffs/day and montelukast 10 mg/day. She stopped using systemic steroids, and daily use of the inhaler was reduced to 6 puffs/day on April 15.

On June 10, peripheral blood eosinophil count was 228/ μ L, and serum total IgE was 155 IU/mL. Percentage of predicted FEV₁ was 75.00 %, and Asthma Control Test (ACT) score was 13. She agreed to receive the first administration of 100mg mepolizumab(Figure).She had neither history of poor treatment adherence nor comorbidities. On July 9, the blood eosinophil count decreased to 26/ μ L; however, FEV₁ and ACT score was 75.17 % and 16. On November 26, the blood eosinophil count, FEV₁, the ACT score were 20/ μ L, 76.76 %, 25, and daily use of the inhaler was reduced to 4 puffs/day. On May 11, 2019, FEV₁ improved to 79.69 %. The fact that she had been administered mepolizumab monthly for 3 years indicated successful long-term management of her asthma. No adverse effects have been observed.

Benralizumab enables a longer dosing interval than mepolizumab [2].On May 11, 2019, given the benefits of this regimen, she hoped to be given 30 mg benralizumab every 4 weeks for the first 3 doses followed by a fixed-dose administration every 8 weeks. The other regimen was not changed. On July 6, the blood eosinophil count became undetectable. On August 31, she was given the fourth administration. Although the blood eosinophil count remained undetectable, she complained of asthma symptoms (ACT score dropped to 21). On physical examination, slight wheezing during deep breathing on the chest was recorded. Her adherence to the medication and inhaler technique was deemed adequate. The laboratory data showed no findings of respiratory infections. She rejected to be given systemic steroids, and was administered aminophylline. On October 26 and December 21, the blood eosinophil count increased to 335/ μ L, 413/ μ L; in addition, FEV₁ and the ACT score dropped to 70.97 %, 68.01 % and 18, 17. She was administered aminophylline on both days. On December 21, 2019, she refused to continue benralizumab, and instead she agreed to be re-given mepolizumab every 4 weeks. On January 18, 2020, the blood eosinophil count, FEV₁, the ACT score were 281/ μ L, 71.93 %, 20, and her asthma had been gradually controlled.

On August 29, 2020, the blood eosinophil count decreased to $30/\mu\text{L}$; and FEV_1 and the ACT score increased to 79.53 % and 25.

This is an uncommon eosinophilic asthma patient, who, despite showing response to mepolizumab, does not indicate such response to benralizumab. On the contrary, we've reported eosinophilic asthma responded to benralizumab after failure to respond to mepolizumab [3]. Three efficacy endpoints were identified in the present patient as reported [3]. Namely, blood eosinophil count has been approved as a predictive biomarker for the efficacy of anti-IL-5 therapy in eosinophilic asthma patients [4], and blood eosinophil count was the first criterion. Based on the guideline by the UK National Institute for Health and Care Excellence, which has indicated to use spirometry first to improve diagnosis of asthma [5], an improvement of lung function presented the second treatment response criterion. As the third, we selected the ACT scoring [3]. After the first administration of mepolizumab, a rapid reduction in blood eosinophil count was observed in the patient as reported [3]. On the other hand, the restarting administration of mepolizumab induced a slower reduction. Recent paper presented two patients with severe eosinophilic asthma showed secondary loss of response to mepolizumab after 2-year treatment [6], but not in the present patient. Assessing the efficacy of benralizumab after five administrations would be difficult. The patient refused to continue benralizumab, and she was re-given mepolizumab instead. Therefore, potential explanations for our findings are followed. First, benralizumab BORA phase III extension trial showed anti-drug antibodies to benralizumab were developed in 10% of patients given every 4 weeks and in 12% given every 8 weeks, which didn't affected drug efficacy outcome [7]. Measurement of anti-drug antibody to benralizumab is not available in the laboratory, and it is unclear in our case. However, benralizumab has been shown to fully deplete blood eosinophils [8] as seen in the patient, and a sudden rise in the blood eosinophil count on the treatment might be used as a

biomarker of the antibody development. Second, it is known that IL-5 is not only produced by CD4+ lymphocytes, but also type 2 innate lymphoid cells that reside in the airways [9]. Local eosinophilopoiesis may be the predominant process, and after 3-year mepolizumab administration, benralizumab may not make relevant blockades of the eosinophilopoiesis [10].

In conclusion, to our best of knowledge, this is the first case report with eosinophilic asthma represented a response to mepolizumab, but not to benralizumab. So, taking our previously reported patient who represented vice-versa [3] into consideration, global investigation of the detailed characterization of eosinophilic asthma is highly required for identification of responders to new biologic treatments.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical disclosures

Institutional ethics committee approved this study and written informed consent from each individual was obtained before the study.

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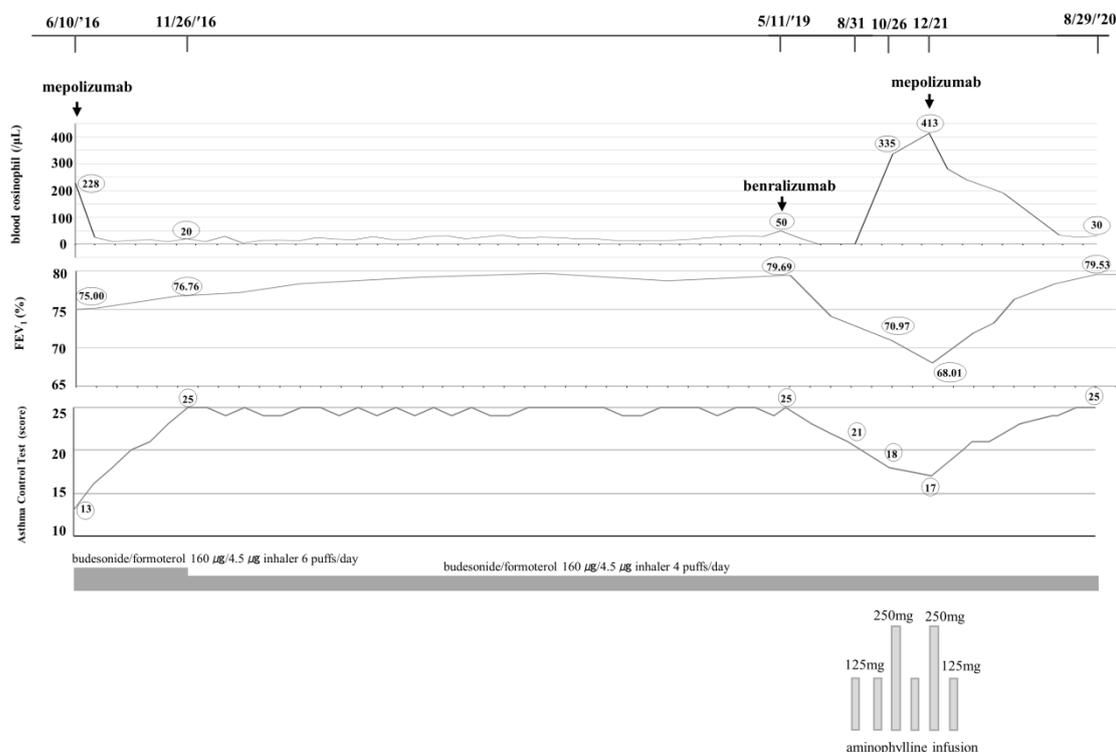
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Figure legends

Figure 1. Clinical course of a patient diagnosed with eosinophilic asthma.



After initiation of monthly mepolizumab on June 10, 2016 (peripheral blood eosinophil count, percentage of predicted FEV₁, and the ACT score were 228/μL, 75.00 %, and 13), she remained controlled for 3-year administrations. On May 11, 2019 (the blood eosinophil count, FEV₁, and the ACT score were 50/μL, 79.69 %, and 25), she was administered benralizumab. Although the blood eosinophil count became undetectable, the pulmonary symptoms have been worse (FEV₁ and the ACT score dropped to 68.01 % and 17). In parallel, the blood eosinophil count increased to 413/μL, which indicated un-sustained response to benralizumab. On December 21, 2019, she has started to be re-given mepolizumab monthly, and her asthma has gradually been controlled. On August 29, 2020, the blood eosinophil count decreased to 30/μL; and FEV₁ and the ACT score increased to 79.53 % and 25.